



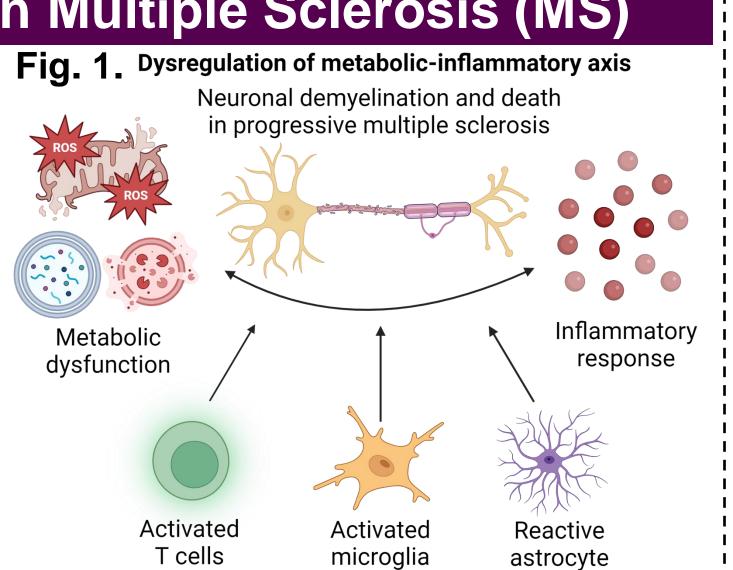
## Dysregulation of the Metabolic-Inflammatory Axis in Progressive Multiple Sclerosis

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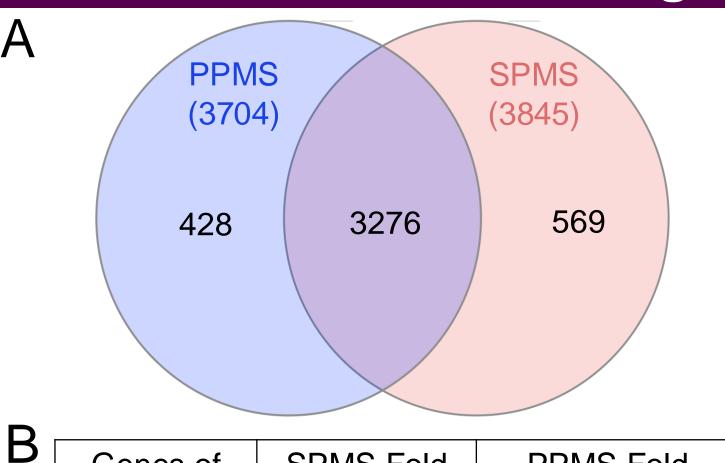
#### Metabolic-Inflammatory Axis in Multiple Sclerosis (MS)

- Recent studies have suggested that disruptions in metabolic processes such as mitochondrial activity as well as autophagy and lysosomal functions play a critical role in the pathogenesis of progressive multiple sclerosis (MS) by compromising energy production and waste clearance<sup>1-3</sup>.
- Metabolic dysfunctions such as elevated oxidative stress intensify inflammatory responses within the central nervous system, leading to demyelination and progressive neuronal loss<sup>4,5</sup>.

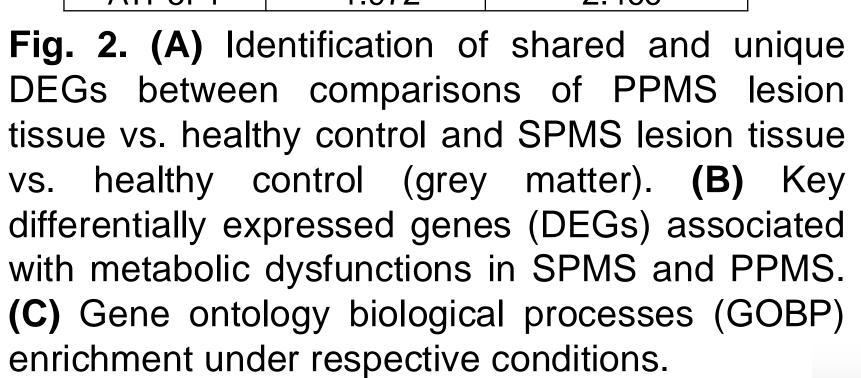


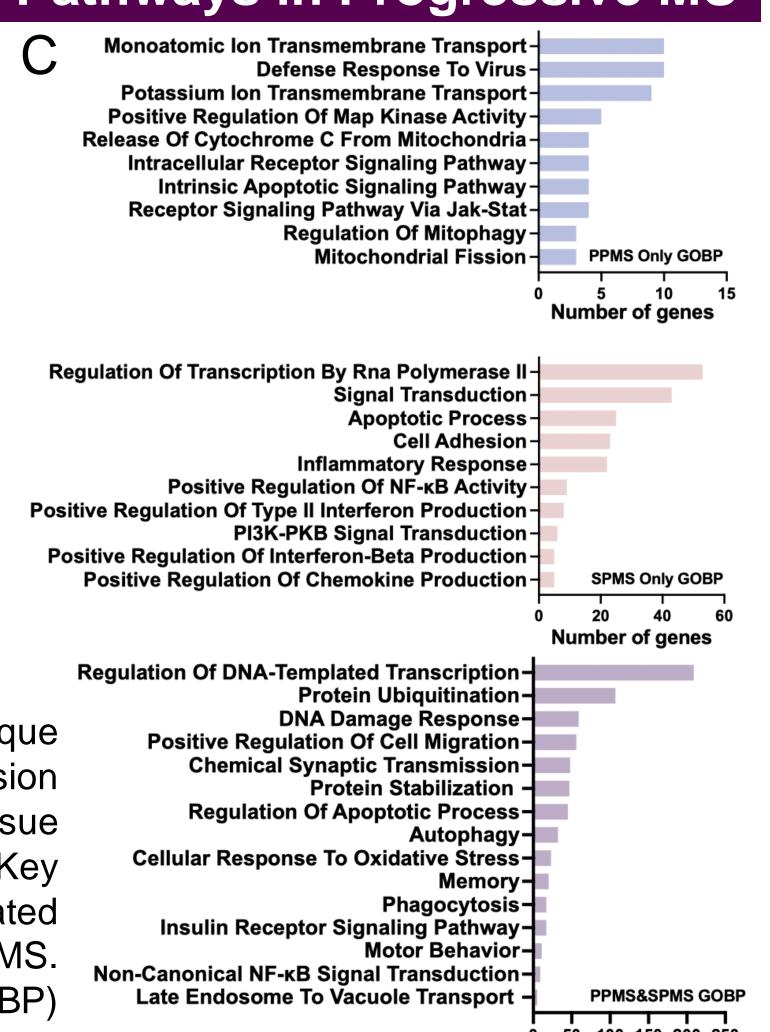
#### Computational to Experimental: Uncovering MS Mechanism (3) Experimental (1) Data Mining: (2) Bioinformatics (4) Therapeutic Identification of **Validation**: Human **Analysis:** WGCNA Intervention: **DEGs** Postmortem MS & Pathway Analysis Lysosome-acidifying **Brain Tissue** nanoparticles (AcNPs) 10000 20000 30000 40000

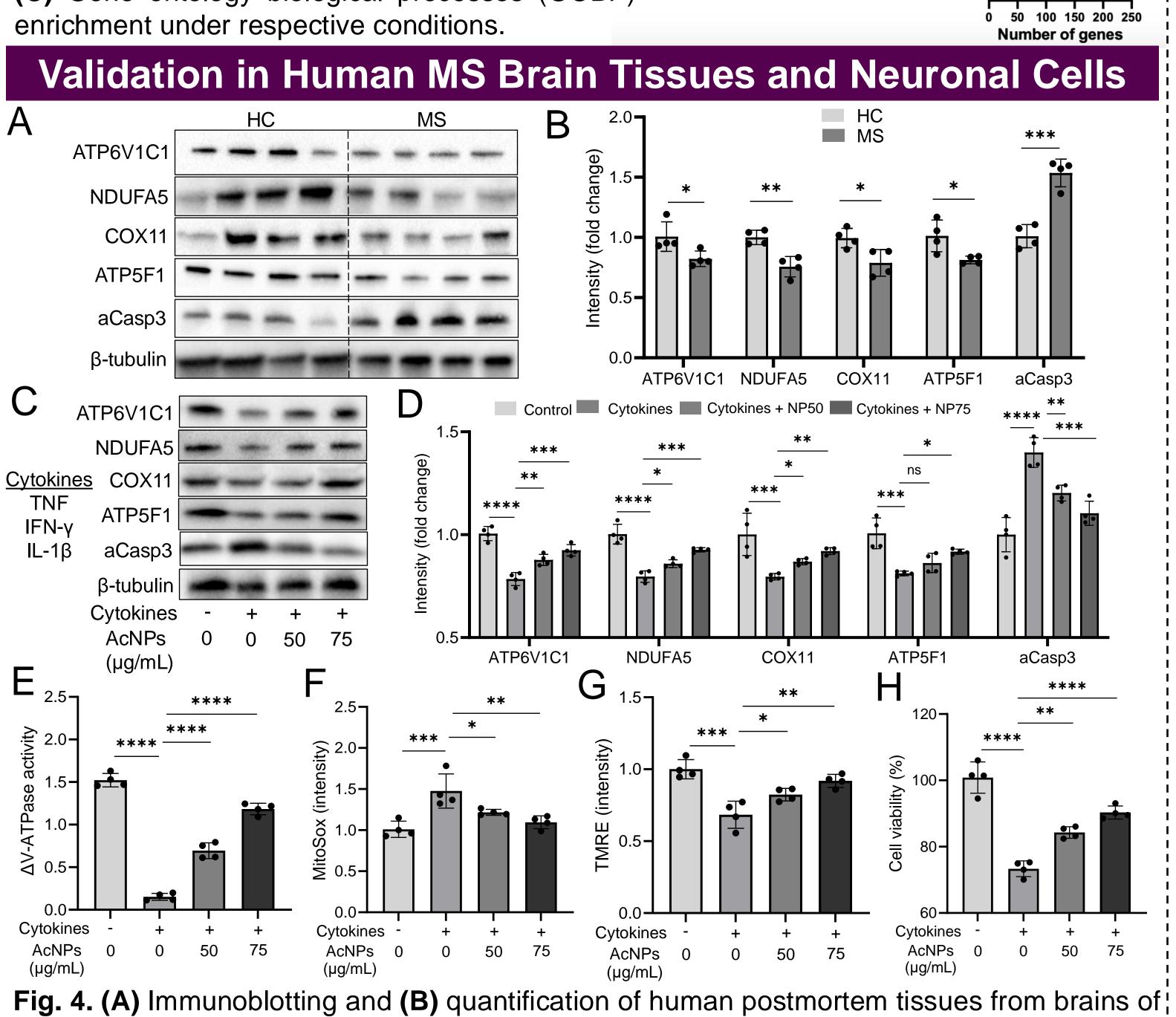
#### Distinct and Shared Biological Pathways in Progressive MS



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	Genes of	SPMS Fold	PPMS Fold
	Interest	Change (log <sub>2</sub> )	Change (log <sub>2</sub> )
	ATP6V1C1	-1.722	-2.310
	NDUFA5	-2.086	-2.168
	COX11	-2.467	-2.505
	ATP5F1	-1.972	-2.466

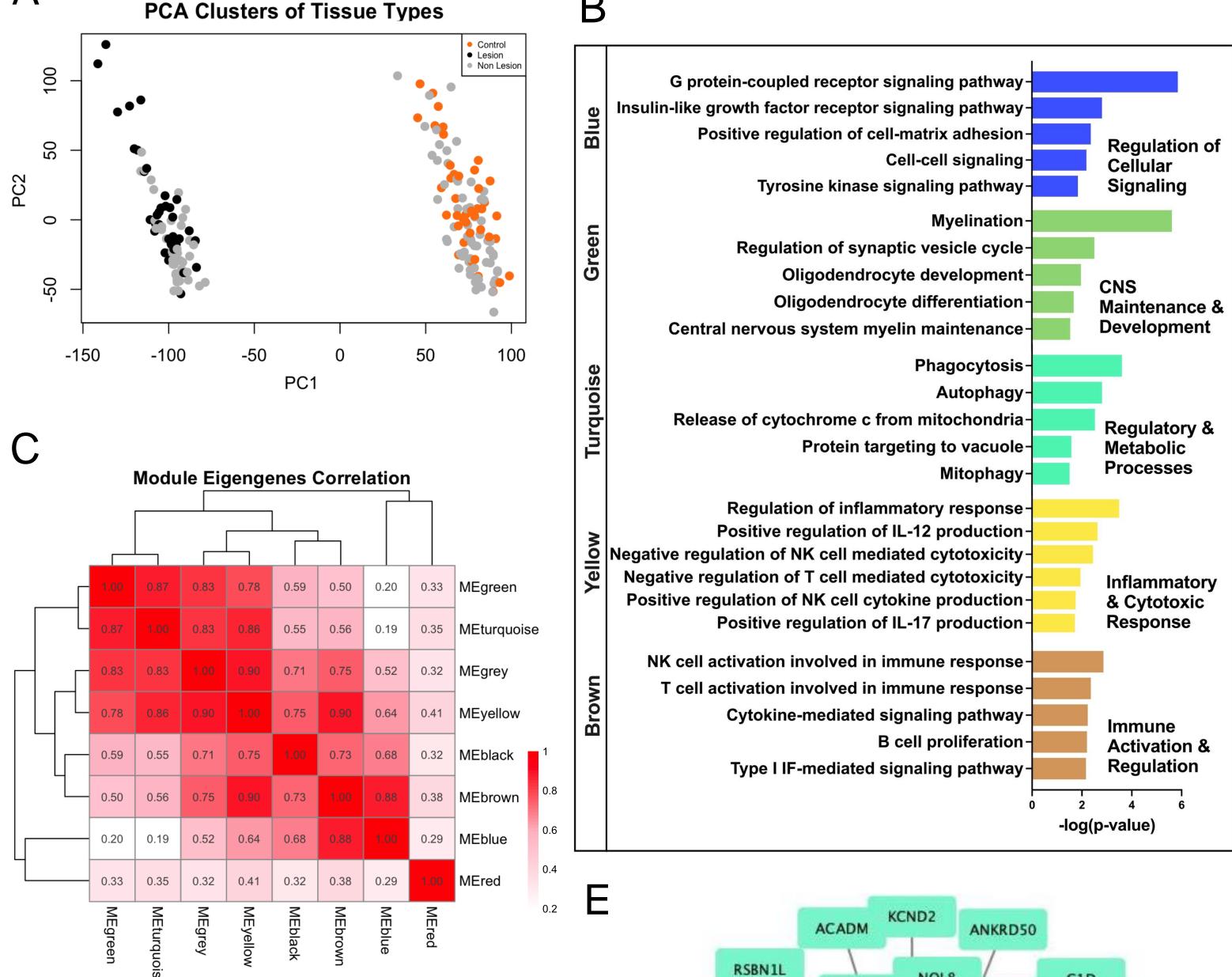


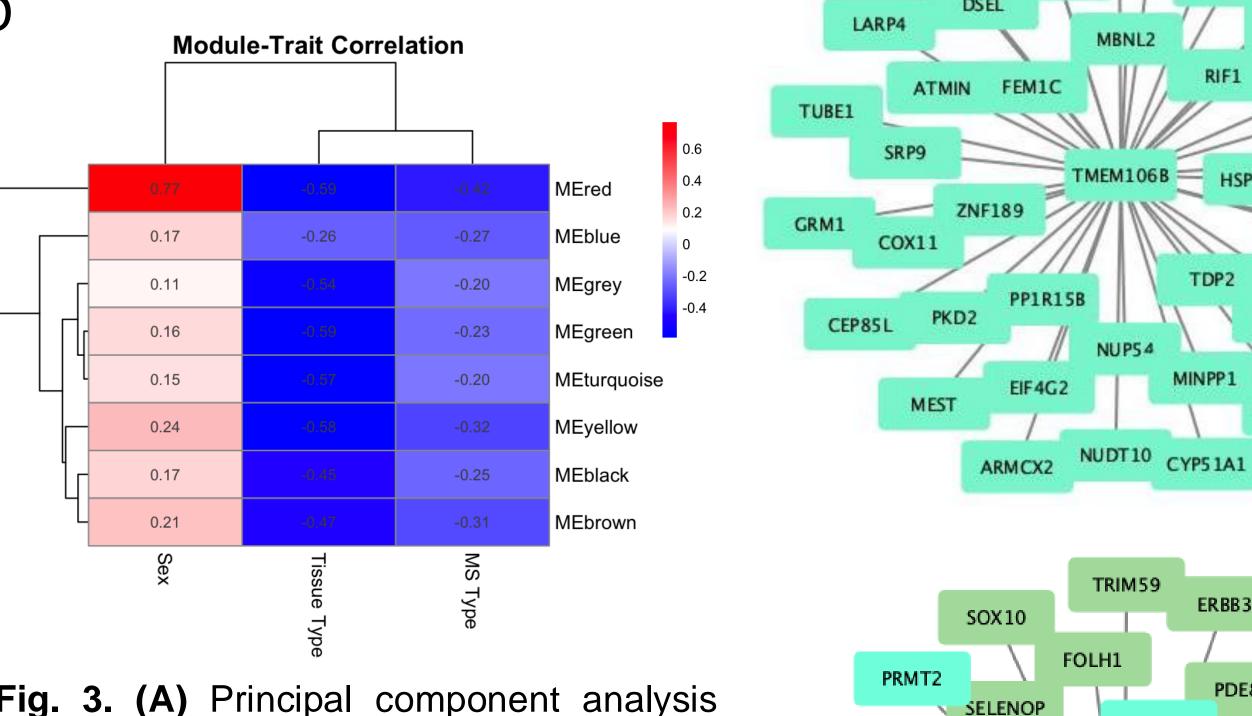




**Fig. 4. (A)** Immunoblotting and **(B)** quantification of human postmortem tissues from brains of healthy control (HC) and MS patients. **(C)** Immunoblotting and **(D)** quantification of SH-SY5Y neuronal cells stimulated with inflammatory cytokines TNF, IFN-γ and IL-1β, with and without lysosome-targeting acidic nanoparticles (AcNPs). **(E)** Lysosomal V-ATPase activity, **(F)** mitochondrial superoxide (MitoSox) production, and **(G)** mitochondrial membrane potential (TMRE), and **(H)** cell viability of SH-SY5Y cells under different treatment conditions.

#### Interconnected Gene Modules in MS Lesions





(A) Principal component analysis (PCA) of grey matter samples from MS lesion, MS non-lesion, and controls. (B) GOBP terms reflective of the key biological pathways under each WCGNA module. (C) illustrating the correlation Heatmap module eigengenes (ME). **(D)** between displaying the significance of Heatmap correlation phenotypes between modules. (E) Visualization of the hub genes TMEM106B (turquoise module) LAMP2 their (green module) interconnected modules and genes.

# FOLH1 PRMT2 PDE8A SIC39A8 GREM1 PLEKHH1 PLEKHH1 PLEKHH1 PLEKHH1 PLEKHH1 PLEKHH1 PHLDB1 CD22 CLDN11 ERMN SLC01A2 RHOG C21orf91 EPS8 COL4A5 HSPA2 AIF1L ERBN FAM107B ABCA8 SP1 FAM107B ABCA8 FOLH1 PDE8A EVIZA WASF2 LAYN TMEM144 ANLN CD22 AIF1L FAM107B ABCA8 SP1

HSP90B1

STX2

#### Relevant Publications from the Lab

- (1) O'Connor LM et al. Integrative multi-omics and systems bioinformatics in translational neuroscience: A data mining perspective. *J Pharm Anal*. 2023;13(8):836-850.
- (2) O'Connor LM et al. Data Mining of Microarray Datasets in Translational Neuroscience *Brain Sciences*. 2023;13(9):1318.
- (3) Pitt D et al. Toward precision phenotyping of multiple sclerosis. *Neurol Neuroimmunol & Neuroinflamm*. 2022;9(6) (4) Lo CH et al. Astrocyte heterogeneity in multiple sclerosis: current understanding and technical challenges. *Front Cell Neurosci*. 2021;15:726479.

#### **Summary and Future Work**

- Metabolic and inflammatory pathways are differentially regulated in progressive MS, suggesting a crosstalk within the metabolic-inflammatory axis.
- Future work: (1) Dissect cell-type specific contributions to metabolic dysregulation &
- (2) Develop novel therapies for treatment of progressive MS

  Acknowledgements: We thank Asst Prof Anna Barron for hosting Dr Chih Hung Lo in LKCMedicine as a Dean's Postdoctoral Fellow. This study was supported by a Dean's Postdoctoral Fellowship and a Mistletoe Research Fellowship awarded to Dr Chih Hung Lo. References: (1) Misrielal et al., Front Cell Neurosci. 2020;14:603710; (2) Blagov et al., Int J Mol Sci. 2022;23(21):12725; (3) González-Jiménez et al., Int J Mol Sci. 2022;23(15):8116 (4) Wang et al., J Neuroinflammation. 2024;21(28); (5) Al-kuraishya et al., Autophagy. 2024;20(2):259.